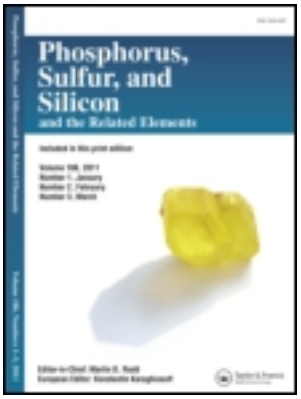

Phosphorus, Sulfur, and Silicon and the Related Elements

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Preparation of α-Ketophosphonate Derivatives and Their Application in the Synthesis of 1-(N-Alkylcarbamoyl)-1-(diethoxyphosphoryl)alkyl Benzoates via Passerini Reaction

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PREPARATION OF α-KETOPHOSPHONATE DERIVATIVES AND THEIR APPLICATION IN THE SYNTHESIS OF 1-(*N*-ALKYLCARBAMOYL)-1-(DIETHOXYPHOSPHORYL)ALKYL BENZOATES VIA PASSERINI REACTION

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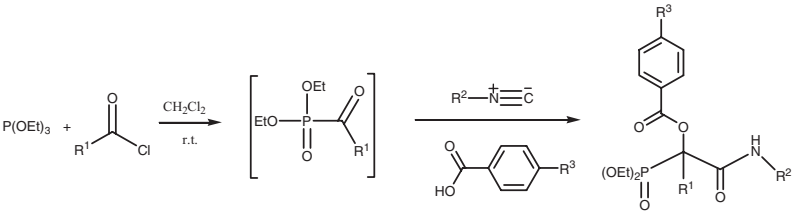
GRAPHICAL ABSTRACT



Abstract *The Passerini reaction of α-ketophosphonates, isocyanides, and benzoic acid derivatives leads to 1-(N-alkylcarbamoyl)-1-(diethoxyphosphoryl)alkyl benzoates in one step at room temperature. The structures of products were assigned on the basis of their ^{1}H NMR, ^{13}C NMR, ^{31}P NMR, and IR spectroscopic data.*

Keywords Benzoic acid derivative; isocyanide; α-ketophosphonate; Passerini reaction

INTRODUCTION

Multicomponent reactions (MCRs) are defined as one-pot reactions in which three or more reactants react to form a single product.[1–3] MCRs are well considered because of their atom economy, facile execution, straightforward reaction design, and convergence. Isocyanides play a basic role in MCRs. The most popular isocyanide-based multicomponent reactions (IMCRs) are the Passerini three component reaction (P-3CR) and the Ugi four-component reaction (U–4CR).[4–6] A remarkable feature of IMCRs is their capability to generate multifunctional compounds from simple monofunctional reactants. Indeed, the large number of different scaffolds now available mostly rests on these two IMCRs

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and their combination with other types of reactions.[7–12] In a Passerini reaction, an isocyanide reacts with an oxo compound in the presence of a carboxylic acid to form an α-acyloxycarboxamide in one step. The Passerini reactions are beginning to find utility in the drug discovery process, and total syntheses of biologically relevant natural products.[13]

Organophosphorus compounds have been extensively employed in organic synthesis as useful reagents, as well as ligands, in a number of transition metal catalysts.[14–27] α-Ketophosphonates are a special group of organophosphorus compounds. The proximity of carbonyl and phosphoryl groups affects the physical, chemical, and biological properties of these compounds. The electron-withdrawing nature of both the carbonyl and the phosphoryl groups confers increased reactivity on both groups and on the bond linking them, which have been exploited synthetically in diverse ways.[28]

Towards some nucleophilic reagents, e.g., hydroxylamine, they behave as ketones, and lead to the formation of oximes, whereas towards most nucleophiles they act as activated carboxylic acid derivatives, with the dialkylphosphoryl group serving as leaving group.[29–31]

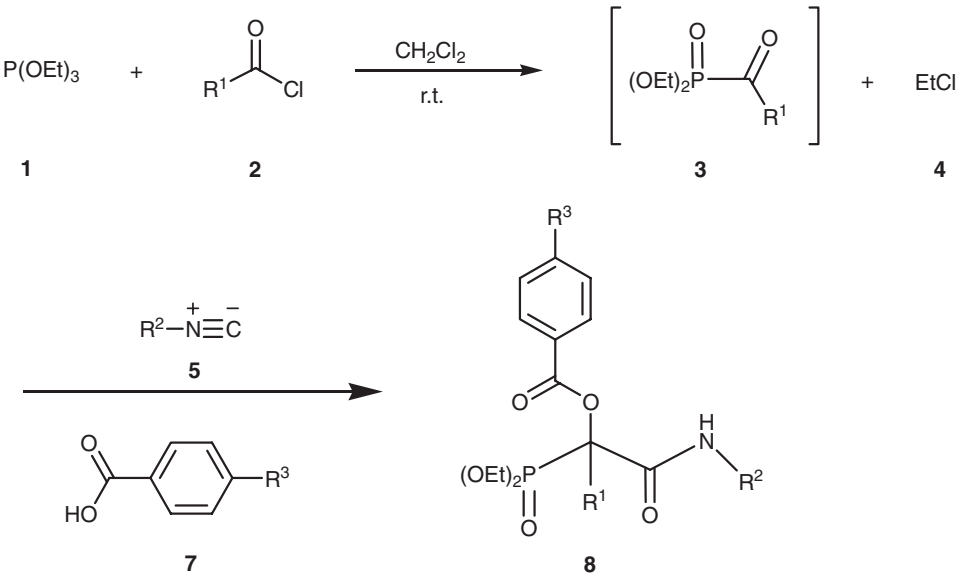
In addition to the traditional Arbuzov method, a number of alternative syntheses of α-ketophosphonates, e.g., the rearrangement of 1-halo-1,2-epoxyphosphonates, oxidation of α-hydroxyphosphonates, nitrosation of carbanionic centers in the α-position of phosphonates, oxidation of α-diazophosphonates, and hydrolysis of dithianes, are now reported in the literature.[32–36]

α-Ketophosphonates have been shown to be synthetically versatile molecules and have been used for the synthesis of a number of phosphorus-containing and nonphosphorus-containing molecules. The ketonic character of the C=O bond of an α-ketophosphonate functionality is demonstrated through a number of reactions including their reaction toward reducing and Vilsmeier–Hack reagents, reductive amination, and olefination.[37–40]

In continuation of our previous studies on heteroatom-containing organic compounds,[41–94] in this article we describe the Passerini reaction of alkyl and aryl substituted α-ketophosphonates with benzoic acid derivatives at room temperature.

RESULTS AND DISCUSSION

α-Ketophosphonates **3** were synthesized based on a literature report.[18] The Passerini reaction of alkyl substituted α-ketophosphonates is completed in 24 hours, but the Passerini reaction of aryl substituted α-ketophosphonates requires more time. On the other hand, alkyl substituted α-ketophosphonates are more reactive than aryl substituted α-ketophosphonates in Passerini reactions, and also the yields of aryl substituted α-ketophosphonates are lower than those of alkyl substituted α-ketophosphonates, which is probably due to steric effects (Scheme 1 and Table 1). The structures of the products **8a–g** were deduced from their IR, ^{1}H NMR, ^{13}C NMR, and ^{31}P NMR spectra and elemental analyses. For example the IR spectrum of **8a** showed strong absorptions at 3334, 1735, 1682 and 1274 cm^{-1} indicating the presence of NH, C=O(ester), C=O(amide), and P=O functional groups, respectively. The ^{1}H NMR spectrum of **8a** exhibited a multiplet for the cyclohexyl ring (δ = 1.0–1.8 ppm), a multiplet for the CH cyclohexyl proton (δ = 3.77 ppm), two triplets for CH_3 moieties of the phosphonate ester (δ = 1.31 and 1.35 ppm, $^{3}J_{H\text{-}H}$ = 7.2 Hz), and a multiplet for two CH_2OPO groups (δ = 4.1–4.3). The CH_3 protons appeared as a doublet at 1.9 ppm ($^{3}J_{HP}$ = 15.5 Hz) due to coupling with the phosphorus atom. The NH proton was observed as a doublet at 6.31 ppm ($^{3}J_{HH}$ = 8.0 Hz). In the signals related to aromatic protons, the *ortho*-protons were observed as doublet at δ = 7.99 ($^{3}J_{HH}$ = 8.2 Hz), the *meta*-protons



Scheme 1 Synthesis of 1-(*N*-alkylcarbamoyl)-1-(diethoxyphosphoryl)alkyl benzoates **8** (see Table 1).

were observed as triplet at $\delta = 7.41$ ($^3J_{HH} = 7.7$ Hz), and the *para*-proton was observed as a triplet at $\delta = 7.55$ ppm ($^3J_{HH} = 7.2$ Hz).

The ^{13}C NMR spectrum of **8a** showed six distinct resonances in agreement with the cyclohexyl carbon atoms and four resonances for aromatic carbon atoms. The methyl groups of the phosphonate esters were observed as two doublets at δ 16.4 and 16.5 ppm ($^3J_{CP} = 5.7$ Hz) and the CH_2O moieties of the phosphonate ester appeared as doublets at δ 63.9 and 64 ppm ($^2J_{CP} = 6.3$ Hz). The methyl and the quaternary carbon atoms were observed as doublets at δ 18.1 ($^3J_{CP} = 2.5$ Hz) and 80.5 ($^1J_{CP} = 157.2$ Hz), respectively. The ester and amide carbonyl signals were observed as doublets at δ 164.1 (d, $^3J_{CP} = 13.8$ Hz) and 165.3 (d, $^2J_{CP} = 2.5$ Hz), respectively. On the other hand, the ^{13}C NMR spectrum of compounds **8e–g**, showed four signals as a doublet at δ 120–140 ppm attributable to the phenyl ring R^1. The ^{31}P NMR spectrum of compounds **8a–g** showed one signal at δ 16–20 ppm.

Table 1 Synthesis of 1-(*N*-alkylcarbamoyl)-1-(diethoxyphosphoryl)alkyl benzoates **8** from α-ketophosphonates and benzoic acid derivatives **7** (Scheme 1)

Entry	R^1	R^2	R^3	Yield of **8** (%)	Reaction time
a	Me	C_6H_{11}	H	75	24 h
b	Me	t-Bu	H	72	24 h
c	Me	t-Bu	Me	70	24 h
d	Me	t-Bu	Cl	71	24 h
e	Ph	C_6H_{11}	H	57	60 h
f	Ph	t-Bu	H	52	60 h
g	Ph	C_6H_{11}	Me	55	60 h

CONCLUSIONS

We found that the reaction of alkyl and aryl substituted α-ketophosphonates with isocyanides in the presence of benzoic acid derivatives occurs under neutral conditions. The reported method offers a mild and simple route for the preparation of 1-(*N*-alkylcarbamoyl)-1-(diethoxyphosphoryl)alkyl benzoates.

EXPERIMENTAL

Starting materials and solvents were obtained from Merck (Germany) and Fluka (Switzerland) and were used without further purification. IR spectra (thin films) were measured on a Shimadzu IR-460 spectrometer. ^{1}H NMR, ^{13}C NMR, and ^{31}P NMR spectra were measured ($CDCl_3$) with a Bruker DRX-250 Avance spectrometer at 250.0, 62.9, and 101.2 MHz, respectively. Elemental analyses were performed using a Heraeus CHN-O-Rapid analyzer. Layer chromatography plates were prepared from Merck silica gel.

General Procedure for the Preparation of Compounds 3 and 8

A solution of 0.166 g (1 mmol) triethyl phosphite in 5 mL CH_2Cl_2 was added dropwise to a magnetically stirred solution of acyl chloride **2** (1 mmol) in dry CH_2Cl_2 (5 mL) at 0°C over 15 min. The mixture was then allowed to warm to r.t. and stirred for 30 min. Benzoic acid **7** (1 mmol) and isocyanide **5** (1 mmol) were then added. The mixture was stirred for 24 h (60 h for **3e**, **3f**, and **3g**) at r.t. The solvent was removed under reduced pressure, and the residue was purified by layer chromatography on silica gel (SiO_2, petroleum ether/ethyl acetate 10:2) to afford the pure compounds. The characterization data of compounds **8** are given below:

1-(*N*-Cyclohexylcarbamoyl)-1-(diethoxyphosphoryl)ethyl benzoate (8a). Colorless viscous oil, yield: 75%. IR (ν_{max}, cm^{-1}): 3334(NH), 2932, 1735(C=O), 1682(C=O), 1526, 1451, 1274(P=O), 1019. ^{1}H NMR: δ 1.0–1.8 (m, 10H, cyclohexyl), 1.31 (t, 3H, $^3J_{HH}$ = 7.2 Hz, CH_3CH_2OPO), 1.35 (t, 3H, $^3J_{HH}$ = 7.2 Hz, CH_3CH_2OPO), 1.91 (d, 3H, $^3J_{HP}$ = 15.5 Hz, CH_3), 3.77 (m, 1H, CHN), 4.1–4.3 (m, 4H, $2CH_2OPO$), 6.31 (d, 1H, $^3J_{HH}$ = 8.0 Hz, NH), 7.41 (t, 2H, $^3J_{HH}$ = 7.7 Hz, arom), 7.55 (t, 1H, $^3J_{HH}$ = 7.2 Hz, arom), 7.99 (d, 2H, $^3J_{HH}$ = 8.2 Hz, arom). ^{13}C NMR: δ 16.4 (d, $^3J_{CP}$ = 5.7 Hz, CH_3CH_2O), 16.5 (d, $^3J_{CP}$ = 5.7 Hz, CH_3CH_2O), 18.1 (d, $^2J_{CP}$ = 2.5 Hz, CH_3), 24.5, 24.6, 25.4, 32.4, 32.6, 48.5, 63.9 (d, $^2J_{CP}$ = 6.3 Hz, CH_2O), 64.0 (d, $^2J_{CP}$ = 6.3 Hz, CH_2O), 80.5 (d, $^1J_{CP}$ = 157.2 Hz, C), 128.6, 129.5, 129.8, 133.5, 164.1 (d, $^3J_{CP}$ = 13.8 Hz, C=O ester), 165.3 (d, $^2J_{CP}$ = 2.5 Hz, C=O amide). ^{31}P NMR: δ 18.7. Anal. Calcd. for $C_{20}H_{30}NO_6P$ (411.44): C 58.39, H 7.35, N 3.40, found: C 58.62, H 7.51, N 3.62%.

1-(*N*-*tert*-Butylcarbamoyl)-1-(diethoxyphosphoryl)ethyl benzoate (8b). Colorless viscous oil, yield: 72%. IR (ν_{max}, cm^{-1}): 3434 (NH), 2929, 1733(C=O), 1676(C=O), 1526, 1451, 1269(P=O), 1023. ^{1}H NMR: δ 1.25–1.40 (m, 6H, $2CH_3CH_2OPO$), 1.30 (s, 9H, Me_3C), 1.90 (d, 3H, $^3J_{HP}$ = 15.20 Hz, CH_3), 4.15–4.40 (m, 4H, $2CH_2OPO$), 6.25 (s, NH), 7.44 (t, 2H, $^3J_{HH}$ = 7.7 Hz, arom), 7.55 (t, 1H, $^3J_{HH}$ = 7.7 Hz, arom), 8.00 (d, 2H, $^3J_{HH}$ = 7.8 Hz, arom). ^{13}C NMR: δ 16.4 (d, $^3J_{CP}$ = 6.3 Hz, CH_3CH_2O), 16.5 (d, $^3J_{CP}$ = 5.7 Hz, CH_3CH_2O), 17.8 (d, $^2J_{CP}$ = 1.9 Hz, CH_3), 29.0 (Me_3C), 51.6 (Me_3C), 63.9 (d, $^2J_{CP}$ = 6.9 Hz, CH_2O), 64.0 (d, $^2J_{CP}$ = 6.3 Hz, CH_2O), 80.9 (d, $^1J_{CP}$ = 157.2 Hz, C), 128.5, 129.6, 129.8, 133.5, 164.1 (d, $^3J_{CP}$ = 14.4 Hz, C=O ester),

165.2 (d, $^3J_{CP}$ = 2.1 Hz, C=O amide). ^{31}P NMR: δ 19.0. Anal. Calcd. for $C_{18}H_{28}NO_6P$ (385.40): C 56.10, H 7.32, N 3.63, found: C 55.89, H 7.16, N 3.78%.

1-(*N-tert*-Butylcarbamoyl)-1-(diethoxyphosphoryl)ethyl 4-methylbenzoate (8c). Colorless viscous oil, yield: 70%. IR (ν_{max}, cm^{-1}): 3436 (NH), 2922, 1732(C=O), 1688(C=O), 1524, 1455, 1268 (P=O), 1027. ^{1}H NMR: δ 1.28–1.42 (m, 6H, 2CH_3CH_2OPO), 1.32 (s, 9H, Me_3C), 1.92 (d, 3H, $^3J_{HP}$ = 15.5 Hz, CH_3), 2.42 (s, 3H, Me), 4.15–4.40 (m, 4H, 2CH_2OPO), 6.24 (s, NH), 7.26 (d, 2 H, $^3J_{HH}$ = 8.0 Hz, arom), 7.93 (d, 2 H, $^3J_{HH}$ = 8.0 Hz, arom). ^{13}C NMR: δ 16.4 (d, $^3J_{CP}$ = 5.7 Hz, CH_3CH_2OPO), 16.5 (d, $^3J_{CP}$ = 5.7 Hz, CH_3CH_2OPO), 17.8 (d, $^2J_{CP}$ = 2.5 Hz, CH_3), 21.7 (Me), 30.9 (Me_3C), 51.6 (Me_3C), 63.9 (d, $^2J_{CP}$ = 5.7 Hz, CH_2OPO), 64.0 (d, $^2J_{CP}$ = 6.3 Hz, CH_2OPO), 80.8 (d, $^1J_{CP}$ = 160.4 Hz, C), 126.9, 129.2, 129.9, 144.3, 164.1 (d, $^3J_{CP}$ = 12.8 Hz, C=O ester), 165.3 (d, $^2J_{CP}$ = 2.1 Hz, C=O amide). ^{31}P NMR: δ 19.1. Anal. Calcd. for $C_{19}H_{30}NO_6P$ (399.43): C 57.13, H 7.57, N 3.51, found C 57.46, H 7.76, N 3.74%.

1-(*N-tert*-Butylcarbamoyl)-1-(diethoxyphosphoryl)ethyl 4-chlorobenzoate (8d). Colorless viscous oil, yield: 71%. IR (ν_{max}, cm^{-1}): 3393(NH), 2978, 1738(C=O), 1698(C=O), 1526, 1454, 1262 (P=O), 1016, 757. ^{1}H NMR: δ 1.30–1.45 (m, 6H, 2CH_3CH_2OPO), 1.31 (s, 9H, Me_3C), 1.91 (d, 3H, $^3J_{HP}$ = 15.5 Hz, CH_3), 4.19- 4.40 (m, 4H, 2CH_2OPO), 6.28 (s, NH), 7.42 (d, 2 H, $^3J_{HH}$ = 7.6 Hz, arom), 7.96 (d, 2 H, $^3J_{HH}$ = 7.6 Hz, arom). ^{13}C NMR: δ 16.4 (d, $^3J_{CP}$ = 5.7 Hz, CH_3CH_2OPO), 16.5 (d, $^3J_{CP}$ = 5.7 Hz, CH_3CH_2OPO), 18.1 (d, $^2J_{CP}$ = 2.5 Hz, CH_3), 28.5 (Me_3C), 51.7 (Me_3C), 64.0 (d, $^2J_{CP}$ = 5.4 Hz, CH_2OPO), 64.1 (d, $^2J_{CP}$ = 5.4 Hz, CH_2OPO), 81.0 (d, $^1J_{CP}$ = 157.2 Hz, C), 128.1, 128.9, 131.2, 140.0, 163.6 (C=O), 165.0 (C=O). ^{31}P NMR: δ 18.9. Anal. Calcd. for $C_{18}H_{27}NO_6PCl$ (419.85): C 51.49, H 6.48, N 3.33, found C 51.56, H 6.61, N 3.50%.

1-(*N*-Cyclohexylcarbamoyl)-1-(diethoxyphosphoryl)-1-phenylmethyl benzoate (8e). Pale yellow viscous oil, yield: 57%. IR (ν_{max}, cm^{-1}): 3306(NH), 2931, 1742(C=O), 1692(C=O), 1540, 1450, 1266 (P=O), 1031. ^{1}H NMR: δ 1.10 (t, 3H, $^3J_{HH}$ = 7.0 Hz, CH_3CH_2OPO), 1.24 (t, 3H, $^3J_{HH}$ = 7.2 Hz, CH_3CH_2OPO), 1.21–1.94 (m, 10H, cyclohexyl), 3.78 (m, 1H, CHN), 3.93 (m, 2H, CH_2OPO), 4.21 (m, 2H, CH_2OPO), 7.31-7.63 (m, 7H, NH and arom), 7.74 (d, 2H, $^3J_{HH}$ = 6.5 Hz, arom), 8.16 (d, 2 H, $^3J_{HH}$ = 8.0 Hz, arom). ^{13}C NMR: δ 16.1 (d, $^3J_{CP}$ = 5.7 Hz, CH_3CH_2O), 16.3 (d, $^3J_{CP}$ = 6.3 Hz, CH_3CH_2OPO), 18.1 (d, $^2J_{CP}$ = 2.5 Hz, CH_3), 24.5, 24.6, 25.4, 32.4, 32.6, 48.5 (CHN), 64.3 (d, $^2J_{CP}$ = 7.5 Hz, CH_2OPO), 64.7 (d, $^2J_{CP}$ = 6.9 Hz, CH_2OPO), 83.2 (d, $^1J_{CP}$ = 153.5 Hz, C), 126.3 (d, J_{CP} = 4.4 Hz, arom), 128.2 (d, J_{CP} = 2.5 Hz, arom), 128.3 (d, J_{CP} = 2.5 Hz, arom), 128.6, 129.8, 130.0, 133.5, 134.3 (d, J_{CP} = 3.8 Hz, arom), 164.0 (d, $^3J_{CP}$ = 6.3 Hz, C=O ester), 164.3 (d, $^2J_{CP}$ = 5.7 Hz, C=O amide). ^{31}P NMR: δ 16.3. Anal. Calcd. for $C_{25}H_{32}NO_6P$ (473.51): C 63.41, H 6.81, N 2.96, found C 63.55, H 6.95, N 3.11%.

1-(*N-tert*-Butylcarbamoyl)-1-(diethoxyphosphoryl)-1-phenylmethyl benzoate (8f). Pale yellow viscous oil, yield: 52%. IR (ν_{max}, cm^{-1}): 3428(NH); 2976; 1742(C=O); 1697(C=O); 1550; 1451; 1268 (P=O); 1025. ^{1}H NMR: δ 1.13 (t, 3H, $^3J_{HH}$ = 7.0 Hz, CH_3CH_2OPO); 1.25 (t, 3H, $^3J_{HH}$ = 6.8 Hz, CH_3CH_2OPO); 1.39 (s, 9H, Me3C); 4.10 (m, 2H, CH_2OPO); 4.20 (m, 2H, CH_2OPO); 7.26–7.63 (m, 7H, NH and arom); 7.73 (d, 2H, $^3J_{HH}$ = 7.5 Hz, arom); 8.17 (d, 2 H, $^3J_{HH}$ = 7.2 Hz, arom). ^{13}C NMR: δ 16.2 (d, $^3J_{CP}$ = 6.3 Hz, CH_3CH_2OPO); 16.3 (d, $^3J_{CP}$ = 5.7 Hz, CH_3CH_2OPO); 28.5 (Me_3C); 51.9 (Me_3C); 64.3 (d, $^2J_{CP}$ = 7.5 Hz, CH_2OPO); 64.6 (d, $^2J_{CP}$ = 6.3 Hz, CH_2OPO); 81.1 (d, $^1J_{CP}$ = 154.7 Hz, C); 126.5 (d, J_{CP} = 4.4 Hz, arom); 128.2 (d, J_{CP} = 4.1 Hz, arom); 128.3 (d, J_{CP} = 5.0 Hz, arom); 128.6; 129.8; 130.0; 133.5; 134.2 (d, J_{CP} = 3.6 Hz, arom); 163.9

(C=O ester); 164.0 (d, $^2J_{CP}$ = 3.2 Hz, C=O amide). ^{31}P NMR: δ 16.5. Anal. Calcd. for $C_{23}H_{30}NO_6P$ (447.47): C 61.74, H 6.76, N 3.13; found C 61.91, H 6.92, N 3.21%.

1-(*N*-Cyclohexylcarbamoyl)-1-(diethoxyphosphoryl)-1-phenylmethyl 4-methylbenzoate (8g). Pale yellow viscous oil; yield: 55%. IR (ν_{max}, cm^{-1}): 3307(NH); 2930; 1738(C=O); 1689(C=O); 1535; 1449; 1265 (P=O); 1025. ^{1}H NMR: δ 1.11 (t, 3H, $^3J_{HH}$ = 7.0 Hz, CH_3CH_2OPO); 1.24 (t, 3H, $^3J_{HH}$ = 7.3 Hz, CH_3CH_2OPO); 1.21–2.10 (m, 10H, cyclohexyl); 2.44 (s, Me); 3.84 (m, 1H, CHN); 3.96 (m, 2H, CH_2OPO); 4.20 (m, 2H, CH_2OPO); 7.26–7.53 (m, 6H, NH and arom); 7.74 (d, 2H, $^3J_{HH}$ = 7.2 Hz, arom); 8.05 (d, 2H, $^3J_{HH}$ = 8.0 Hz, arom). ^{13}C NMR: δ 16.2 (d, $^3J_{CP}$ = 5.7 Hz, CH_3CH_2OPO); 16.3 (d, $^3J_{CP}$ = 6.3 Hz, CH_3CH_2OPO); 21.8 (Me); 24.4; 24.6; 25.5; 32.5; 32.6; 48.5 (CHN); 64.3 (d, $^2J_{CP}$ = 7.5 Hz, CH_2OPO); 64.7 (d, $^2J_{CP}$ = 6.9 Hz, CH_2OPO); 83.1 (d, $^1J_{CP}$ = 151.0 Hz, C); 126.4 (d, J_{CP} = 3.8 Hz, arom); 128.2 (d, J_{CP} = 3.8 Hz, arom); 128.6; 129.3; 130.0; 130.1; 134.3 (d, $^3J_{CP}$ = 3.8 Hz, arom); 144.4 163.7 (d, $^3J_{CP}$ = 6.1 Hz, C=O ester); 164.1 (d, $^2J_{CP}$ = 5.8 Hz, C=O amide). ^{31}P NMR: δ 16.3. Anal. Calcd. for $C_{26}H_{34}NO_6P$ (487.54): C 64.05, H 7.03, N 2.87; found C 63.94, H 7.23, N 2.68%.

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